IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	**MDL No. 2:14-mn-02502-RMG**
	)	**This document relates to:**
	)	*All actions*

PFIZER'S SUPPLEMENTAL DOSE BRIEF IN FURTHER SUPPORT OF ITS MOTION TO EXCLUDE PLAINTIFFS' EXPERT TESTIMONY ON GENERAL CAUSATION

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PRELIMINARY STATEMENT

This Court correctly held that "dose certainly matters, and Plaintiffs must have expert testimony that Lipitor causes, or is capable of causing, diabetes at particular doses." CMO 49 [1197] at 11. The Court permitted the parties to serve supplemental expert reports and take follow-up depositions as to "whether Lipitor causes diabetes at dosages of 10 mg, 20 mg, 40 mg, and/or 80 mg." *Id.* Plaintiffs served supplemental reports from Drs. Singh, Quon, and Roberts, and Pfizer took their depositions. Pfizer then served supplemental reports from Drs. Hennekens, Elasy, and Waikar, and Plaintiffs waived their depositions.[1] Plaintiffs have still failed to provide reliable evidence that Lipitor causes diabetes at any dose.

Only randomized clinical trials can sufficiently control for confounding and bias to show a causal relationship, if any, between Lipitor and diabetes. They do not. [redacted]; *see* Roberts Supp. Tr. (Ex. 97) at 437:14-18; [redacted] ASCOT studied diabetes as a prespecified endpoint and found no statistically significant risk at 10 mg. Navarese conducted a network meta-analysis of all clinical trial data and found no statistically significant association at 10 mg. Singh Tr. [972-3] at 191:25-192:19, 200:22-201:8.[2] Nor does Dr. Singh's indirect meta-analysis of two clinical trials show a statistically significant association at 10 mg. *See* Singh Supp. Rpt. (Ex. 92) at 28.

The absence of a reliable basis for causation at 10 mg is fatal to establishing causation at 20 mg and 40 mg, where there are no clinical trial data. Dr. Singh, Plaintiffs' primary general causation expert, freely admits that [redacted]

At 80 mg, Plaintiffs point to *post hoc* analyses of clinical trials, the results of which are

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[1] The supplemental reports from Drs. Singh, Quon, and Roberts are attached as Exs. 92, 93, and 94, and the transcripts of their supplemental depositions are attached as Exs. 95, 96, and 97. The supplemental reports from Drs. Hennekens, Elasy, and Waikar are attached as Exs. 98, 99, and 100.

[2] Navarese et al., *Meta-Analysis of Impact of Different Types and Doses of Statins on New-Onset Diabetes Mellitus*, 111 Am. J. of Cardiol. 1123, 1127 (2013) [972-48].

inconsistent. Two of the four clinical trials report no statistically significant association. Nor does the Navarese meta-analysis find a statistically significant association at 80 mg. Singh Tr. [972-3] at 191:25-192:19, 200:22-201:8.[3]

Plaintiffs' experts cannot properly resort to the observational studies at issue to show a valid statistical association, much less causation. As to the observational studies on which they rely – Cederberg, Culver, Carter, and Chen – Dr. Singh admits that [redacted]

Among other things, observational studies of statins and diabetes are subject to confounding by indication. [redacted] Hennekens Supp. Rpt. (Ex. 98) at 3-5, 13-15, 17-25, 28, 31, 33, 36-37, 39-40, 43; Elasy Supp. Rpt. (Ex. 99) at 4, 9-10, 12; Waikar Supp. Rpt. (Ex. 100) at 6. Confounding by indication arises because patients who are prescribed statins are inherently different from those who are not and because physicians are more likely to prescribe statins to patients at a higher risk for diabetes since they are the same patients who are at a higher risk for cardiovascular disease (the chief indication for which statins are prescribed). Given the high degree of overlap in the major risk factors for diabetes and cardiovascular disease, the confounding by indication in any observational study at issue, no matter how well designed or conducted, can be larger than the alleged effect sizes being explored. Thus, confounding by indication cannot be ruled out as a plausible explanation for any observed association. Such studies are hypothesis formulating, not hypothesis testing.

Nor can the glucose change data reliably show causation. These data are a full step removed from the issue before this Court and do not "fit" since they address glucose changes, not diabetes. They also come from short-term studies, typically involving patients with baseline

[3] Navarese (2013) [972-48] at 1127.

glucose abnormalities. Dr. Quon relies on a handful of such studies. Those studies are not only contrary to the evidence from clinical trials, but they are also contradicted by the majority of the physiologic literature on Lipitor and diabetes, which [redacted] Dr. Quon ignores the statement in his peer-reviewed paper that "[i]t is not clear why [Lipitor] has beneficial metabolic actions in some studies but not in others."[4] There is a gross disparity between his peer-reviewed published statements and his litigation opinion.

Likewise, Plaintiffs' experts cannot base a reliable general causation opinion on data from the Lipitor 1999 and 2001 Safety Updates. As this Court recognized in rejecting Dr. Jewell's NDA opinion, the use of single glucose change measurements to show causation of diabetes is suspect at best. *See* CMO 54 [1258] at 7. While Dr. Singh acknowledges the limitations of these data, Drs. Quon and Roberts try to rely on them to show causation. [redacted] Rather, for questions about the data, [redacted] Further, because Plaintiffs' experts failed to analyze the underlying patient data, they did not address confounding due to baseline glucose abnormalities, which this Court identified as a fatal flaw in Dr. Jewell's opinion. CMO 54 [1258] at 10. [redacted]

Plaintiffs' experts' general causation testimony is beset by many unbridgeable analytical gaps between the existing data and their opinions that Lipitor causes diabetes. *General Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). It must therefore be excluded.

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[4] Koh et al., *Differential metabolic effects of distinct statins*, 215 Atherosclerosis 1 (2011) (Ex. 101).

PLAINTIFFS' EXPERTS' OPINIONS ARE METHODOLOGICALLY UNSOUND

All three of Plaintiffs' experts go beyond and contradict the evidence from randomized clinical trials and try to show general causation based on subordinate data. They cannot reliably do so. For a common set of reasons, their attempts are methodologically unsound. Each expert's opinion also contains other flaws, including results-oriented reversals of prior positions, that warrant exclusion of their testimony as unreliable. A handful of examples for each follows.

Dr. Singh

- Dr. Singh states that "[i]t is difficult to imagine how … 10 mg and 80 mg can increase the risk of diabetes without similar risk seen with … 20 and 40 mg." Singh Supp. Rpt. (Ex. 92) at 33. [redacted]
- Dr. Singh's initial report asserts that "an association greater than 1.5 in epidemiologic studies is considered more likely causal." Singh Rpt. [972-6] at 34; Singh Tr. [972-3] at 349:1-350:20. Yet the observational studies cited by Plaintiffs report risks below his greater than 1.5 threshold. [redacted]
- Despite having acknowledged the problem of "confounding by indication" in his published writings [redacted]
- [redacted] Dr. Singh ignores the Navarese meta-analysis, which found no statistically significant risk at any dose, and which he says was "quite reasonably well conducted" and [redacted] Singh Tr. at 191:20-24; [redacted]
- [redacted]

Dr. Quon

- Dr. Quon co-authored a peer-reviewed paper which noted that 8 of 9 studies on Lipitor did not show an adverse effect on glucose metabolism.[5] Yet in his supplemental report, [redacted]

[5] Koh (2011) (Ex. 101) at 4.

[redacted]

[redacted] *accord* Roberts Supp. Tr. (Ex. 97) at 443:5-7.

- [redacted]

- [redacted] (Nor does Dr. Roberts. Roberts Supp. Tr. at 389:15-17, 499:16-24.) This lack of knowledge presents a huge methodological blind spot in their analyses. One cannot account for confounding by indication if one does not know what it is.

Dr. Roberts

- As for the requirement in CMO 49 that experts describe their methodology, Dr. Roberts said, "[w]ell, with all due respect, this to me sounds very legal, legalesy," Roberts Supp Tr. (Ex. 97) at 357:7-15, and repeatedly described her methodology as "reviewing articles." *Id.* at 357:7-15, 450:11-15, 452:12-14. But that is not a methodology, let alone an objective, testable, or reliable methodology.

- Dr. Roberts previously opined that observational studies produce better data on causation than clinical trials. Roberts Tr. [972-9] at 110:17-111:2, 176:11-18. Asked if she ever heard that "[o]bservational studies may tell us about association but they cannot prove causation," she says she "remember[s] reading" that somewhere. Roberts Supp. Tr. at 489:20-24. In fact, she wrote that in her 2012 book. *Id.* at 490:5-24; Roberts, *The Truth About Statins* 106 (2012) (Ex. 102).

- Dr. Roberts is not an expert in diabetes, epidemiology, or statistics. Roberts Supp. Tr. at 361:5-8, 376:3-5, 389:2-5, 389:21-22. She does not know of confounding by indication, the limits of *post hoc* analysis or cross-sectional study design, or of statistical "power." *Id.* at 389:15-17, 499:16-24, 388:8-15, 390:16-19, 399:15-17.

- Dr. Roberts, remarkably, said she does not believe there is any overlap between the risk factors for diabetes and for heart disease. *Id.* at 392:8-11. She also believes, erroneously, that all the articles she cited controlled for all the important risk factors for diabetes. *Id.* at 396:17-22, 397:14-19, 398:9-15. Yet she later admitted that each study failed to adjust for many risk factors. *Id.* at 509:3-511:19, 526:25-527:5, 539:18-541:1-4, 549:9-551:14, 561:24-563:11, 573:7-574:11.

- Dr. Roberts did not discuss any of the limitations of the observational studies because she "wasn't asked to discuss limitations" and "didn't think it was important." *Id.* at 401:10-16, 402:3-7, 501:11-16, 549:7-8. But causation experts must address why the positive associations reported in these studies "are true associations, and not the result of a study flaw, confounding, bias, or other factor." *In re Zoloft (Sertraline Hydrocloride) Prods. Liab. Litig.*, 2015 WL 7776911, at *16 & n.52 (E.D. Pa. 2015).
- Instead of proffering a dose-specific opinion, Dr. Roberts addresses "whether … Lipitor ***across a dose range*** of 10 to 80 milligrams a day increased the risk of diabetes." Roberts Supp. Tr. at 353:6-11. She does not break out the data at any dose and "can't quantify" any difference between doses. *Id.* at 410:23-411:18. Yet she nevertheless opines that Lipitor "probably doubled" the risk of diabetes "across the dose range." *Id.* at 445:8-14, 446:15-23, 447:7-448:1.
- In contrast to her prior testimony that "increased risk" is not causation, Roberts Tr. [972-9] at 83:4-22, Dr. Roberts now says "the implication" of an increased risk is causation. Roberts Supp. Tr. at 359:20-360:5. To quote Dr. Roberts's 2012 book, "[u]nfortunately, in the realm of medical research, conflating association and causation has all too often led us down the wrong path." *Id.* at 493:1-13; Roberts, *The Truth About Statins* (2012) (Ex. 102) at 191.

In sum, Plaintiffs' experts employ litigation driven methods that contradict their prior statements, both in the published literature and in this litigation, and make other methodological errors that render their general causation opinions unreliable and inadmissible.

PLAINTIFFS' EXPERTS CANNOT RELIABLY SHOW GENERAL CAUSATION

This Court held that where "studies have not found an association at lower dosages," the Court must inquire "whether Plaintiffs can demonstrate that Lipitor is capable of causing diabetes at lower dosages." CMO 49 [1197] at 4. Plaintiffs' experts purport to establish that Lipitor causes diabetes at doses less than 80 mg through clinical trials, observational studies, glucose change data, and the FDA label. None can meet that task.

Data from randomized, placebo-controlled clinical trials are necessary to establish a causal relationship, if any, between Lipitor and diabetes. There is no statistically significant association at any dose less than 80 mg and at 80 mg the clinical trials are inconsistent. The observational studies cited by Plaintiffs' experts cannot establish a valid statistical association due to uncontrollable confounding by indication and other methodological limitations. All of these observational studies should thus "be viewed as simply reformulating the same hypothesis

that has already been formulated by any one of them." Hennekens Supp. Rpt. (Ex. 98) at 25. The glucose change data are internally inconsistent and inconsistent with clinical trial data. Nor is the FDA's label change a reliable basis for causation for mulitple reasons.

Plaintiffs' experts suggest that this data, whatever its limitations individually, collectively establishes general causation. Singh Supp. Rpt. (Ex. 92) at 32-33. It does not and cannot. There are "unbridgeable gaps in the existing totality of evidence" that preclude a finding of general causation. Hennekens Supp. Rpt. (Ex. 98) at 32. Courts have repeatedly rejected the notion that a collection of unreliable evidence may be redeemed or enriched by other unreliable evidence. "[E]xperts 'cannot lump together lots of hollow evidence' and reach a reliable conclusion." *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 577 (W.D. Pa. 2003) (citation omitted). "[T]he data points pulled from each 'type' of evidence are too limited, too disparate and too inconsistent," amounting "to a hollow whole of hollow parts." *Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1040 (S.D. Ill. 2001). Where Plaintiffs' experts offer a methodology individually "based on data insufficient to base a general causation opinion," there is no justification for the belief that "'the aggregate of this evidence presents a stronger scientific basis'" for general causation. *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp. 2d 1046, 1053 (S.D. Ill. 2001) (quoting *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 992 (8th Cir. 2001)). "In summary, the totality of evidence regarding statins and diabetes should be viewed as hypothesis formulating, not hypothesis testing." Hennekens Supp. Rpt. at 24. The insufficiencies in the data proffered by Plaintiffs' experts, singly and in combination, preclude them from reliably showing general causation.

I. THE LIPITOR CLINICAL TRIAL DATA CANNOT RELIABLY SHOW GENERAL CAUSATION

Randomized clinical trials are well recognized as the "gold standard" of epidemiological evidence. *Ref. Man. on Scientific Evid.* (3d ed. 2011) ("*RM (3d)*") at 579-81. This is so because "randomization provides a degree of control of confounding that is not possible to achieve in any observational analytic study." Hennekens Supp. Rpt. (Ex. 98) at 2 (quoting Hennekens & DeMets, *Statistical association and causation; contribution of different types of*

evidence, 306 JAMA 1134, 1135 (2011) (Ex. 103)). To establish small to moderate effects, such as the alleged association between statins and diabetes, large-scale randomized trials designed *a priori* to test that hypothesis are necessary to exclude chance, bias, and confounding as plausible alternative explanations. *Id.* Dr. Quon agrees that to establish a causal relationship, one needs "a randomized, placebo-controlled, blinded study." Quon Tr. [972-2] at 178:23-179:7. So does Dr. Gale. "In terms of establishing a causal relationship … [y]ou rely on your randomized controlled trials." Gale Tr. [972-1] at 219:4-221:1; *see* Hennekens Supp. Rpt. at 2. Here, the randomized clinical trial data do not show general causation at any dose.

A. The Randomized Clinical Trial Data Do Not Show Causation at 10 mg

Statistical significance measures the ability to exclude chance as an explanation for an association, *see RM (3d)* at 579-81, and is important in determining whether a statistical association is "true" or "valid." A general causation analysis begins, but does not end, by "look[ing] for statistically significant associations between medication exposure and [the injury]." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 455 (E.D. Pa. 2014); *accord* CMO 55 [1283] at 7-8. [redacted], this Court has observed that "a finding of statistical significance is very important" to account for the possibility of random error. CMO 55 [1283] at 9.

Yet, as Dr. Singh admits, [redacted] He further admits that the evidence for causation is "less persuasive" at 10 mg than at 80 mg, Singh Supp. Rpt. (Ex. 92) at 31, [redacted] At 10 mg, the pertinent randomized placebo-controlled clinical trial is ASCOT, which studied diabetes as a prespecified adjudicated endpoint, and found no statistically significant association.[6]

[6] Sever et al., *Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac*

Dr. Singh questions ASCOT's results for many of the same reasons as Dr. Jewell. Dr. Singh professes uncertainty over the definitions used by the ASCOT Endpoint Committee and suggests that the adjudication process deprived the study of power. Singh Supp. Rpt. (Ex. 92) at 3-4; [redacted] But he does not identify any flaw in the work of the Endpoint Committee that warrants re-analysis. Moreover, his claims of uncertainty about the ASCOT definitions are entitled to little weight. [redacted] He previously testified that to infer an outcome is a consequence of exposure, the outcome should be adjudicated. Singh Tr. [972-3] at 105:11-15. Thus, while ignoring adjudicated data would allow "for a narrower 95% confidence interval and thus a statistically more precise result due to the inclusion of more endpoints, it is wrong because the point estimate is biased due to the fact that some of the reported endpoints are not confirmed as diabetes." Hennekens Supp. Rpt. (Ex. 98) at 29.

Dr. Singh claims the "lack of statistical significance" in ASCOT's result is due to lack of statistical power. Singh Supp. Rpt. (Ex. 92) at 27. [redacted] But in science, an *ad hoc* hypothesis, such as the one Dr. Singh's advances, is one that is created to explain away facts that refute one's theory and is a methodological infirmity.[7]

Further, it is simply "incorrect to state that there is a bias related to inadequate power that

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Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial, 361 Lancet 1149, 1153 tbl. 3 (2003) [972-26].

[7] *See* Popper, *Conjectures and refutations: The growth of scientific knowledge* 48, ¶ 7 (2002) (Ex. 104).

drives the relative risk, or, indeed, any estimate of effect size, toward the null." Hennekens Supp. Rpt. (Ex. 98) at 29. Nor does Dr. Singh's claim that ASCOT was underpowered withstand scrutiny. ASCOT "included over 10,000 patients taking either [Lipitor] or placebo for approximately 3.3 years," well greater than "other large, adequately powered landmark clinical trials that have sought to establish incident diabetes." Elasy Supp. Rpt. (Ex. 99) at 3. Moreover, Dr. Singh notes that the non-significant ASCOT result of 1.15 (0.91-1.44) "could not rule out as much as a 44% increase in the risk of diabetes," Singh Supp. Rpt. (Ex. 92) at 3, but [redacted] Hennekens Supp. Rpt. at 29-30.

Dr. Singh's criticisms of ASCOT are ultimately of no avail because he does not opine that ASCOT provides reliable affirmative evidence of causation. Rather, in a misplaced attempt at burden shifting, he claims that ASCOT is "unreliable in establishing the safety of 10 mg of [Lipitor] on the risk of diabetes." Singh Supp. Rpt. (Ex. 92) at 3. But it is Plaintiffs' burden to prove "that particular doses of Lipitor are capable of causing diabetes." CMO 49 [1197] at 11.

Finally, Dr. Singh seeks to show a risk at 10 mg through what he initially called a "network meta-analysis" of clinical trials, [redacted] Singh Supp. Rpt. (Ex. 92) at 27-28; [redacted] Yet his analysis, whatever it is called, includes only two Lipitor trials, TNT and SPARCL. Despite stating that "[w]hen available, I will discuss meta-analysis of clinical trials," Singh Supp. Rpt. at 2, Dr. Singh ignores the published Navarese network meta-analysis, which he included in his original report and admits was "quite reasonably well conducted" and [redacted] Singh Tr. [972-3] at 191:20-24; [redacted]. Navarese analyzed all the relevant Lipitor clinical trial data – TNT, IDEAL, SPARCL, ASCOT, and PROVE-IT – and reported no statistically significant association at any dose.[8] In any event, like Navarese, Dr. Singh's "indirect" meta-analysis for 10 mg "is not statistically significant." Singh Supp. Rpt. at 28;

[8] Navarese (2013) [972-48] at 1127.

[redacted]

B. The Absence of Causation at 10 mg Is Dispositive at 20 mg and 40 mg

By Dr. Singh's admission, the [redacted]; Roberts Supp. Tr. (Ex. 97) at 410:23-411:18. He further admits that [redacted]

The primary basis of Dr. Singh's opinion at 20 mg and 40 mg is that he ascribes risks at 10 mg and 80 mg: "It is difficult to imagine how … 10 mg and 80 mg can increase the risk of diabetes without similar risk seen with … 20 and 40 mg." Singh Supp. Rpt. (Ex. 92) at 33. Yet, as this Court recognized, the data at 80 mg cannot be extrapolated down to lower doses. "[A] risk estimate from a study that involved a greater exposure is not applicable to an individual exposed to a lower dose." CMO 49 [1197] at 3 (quoting *RM (3d)* at 613 n.196). Unable to extrapolate down from 80 mg, [redacted]

C. The Clinical Trial Data Cannot Reliably Show Causation at the 80 mg Dose

Plaintiffs cannot reliably show causation at 80 mg based on statistically significant results from *post hoc* analysis of certain clinical trials. The statistical significance of those results is a necessary, but not sufficient, predicate to a reliable general causation analysis. *See* Singh Tr. [972-3] at 220:16-221:8. "[S]imply because the results of an individual randomized trial not designed *a priori* to test the hypothesis, exclude chance … does not necessarily imply the presence of a valid statistical association, let alone a judgment of causality." Hennekens Rpt. [972-14] at 74. Here, the significant results for the 80 mg dose are based on *post hoc* rather than pre-specified analysis, and the clinical trial data are inconsistent in magnitude and significance. *Id.* at 41; *see* Waikar Supp. Rpt. (Ex. 100) at 23. Of the four clinical trials involving Lipitor 80 mg, *post hoc* analysis of only two, SPARCL and TNT, showed a statistically significant

association with newly diagnosed diabetes. Hennekens Supp. Rpt. (Ex. 98) at 9, 24, 27.

Post hoc analysis cannot show causation because it is hypothesis-generating, not hypothesis-testing. A valid statistical association may be inferred only from a "study designed a priori to test a hypothesis after exclusion of chance, bias, and confounding as plausible alternative explanations." Hennekens Supp. Rpt. (Ex. 98) at 2 (quoting Hennekens & DeMets (2011) at 1135). *Post hoc* analyses led to statistically significant results at 80 mg and the factors present in SPARCL and TNT. But such analyses are "hypothesis generating at best" and must "be handled with caution" because "methodological problems arise," Gale Tr. [972-1] at 270:11-271:7, and [redacted] *see* Singh Supp. Rpt. (Ex. 92) at 6. For example, [redacted]

Likewise, consistency within the totality of data is critical to determining whether an association is valid, let alone causal. *See RM (3d)* at 604-05; [redacted] To do otherwise amounts to "cherry-picking" of data, which "does not reflect scientific knowledge, is not derived by the scientific method, and is not 'good science.'" *In re Bextra & Celebrex Mktg. Sales Pracs. & Prods. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007); *accord In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004); *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 425 & n.164 (S.D.N.Y. 2005). Thus, a causation expert who "selectively discuss[es] studies most supportive of her conclusions ... and fails to account adequately for contrary evidence" must be excluded. *Zoloft*, 26 F. Supp. 3d at 460-61.

[redacted] Yet this is precisely what he does, brushing off the inconsistent results in PROVE-IT and IDEAL. Singh Supp. Rpt. (Ex. 92) at 7, 25. Likewise, despite his commitment to consider meta-analysis where available, his supplemental report ignores Navarese, the only published

meta-analysis that did consider the totality of the clinical trial data at 80 mg, but which did not report a statistically significant association at any dose.[9]

Dr. Singh has offered no reliable basis for his invariable decision to favor evidence that supports causation and to discount evidence that does not. Plaintiffs' experts' cherry-picked case for causation at 80 mg cannot pass *Daubert* muster and must therefore be excluded.

II. THE OBSERVATIONAL STUDIES AT ISSUE CANNOT RELIABLY SHOW CAUSATION

Because of the absence of reliable evidence in the clinical trial data of a true association between Lipitor and diabetes, Plaintiffs' experts' supplemental reports focus heavily on the results of observational studies. Yet these studies are marred by uncontrolled and uncontrollable confounding by indication, as well as other limitations, and thus cannot reliably show a valid statistical association, let alone general causation. As the Court has stated, "[i]f confounding factors, bias or random error is the source of the association, rather than a true causal relationship, the logic falls apart. … [O]bservational studies with the potential for confounding and bias may not be sufficient" to establish the relative risk at issue. CMO 55 [1283] at 9. For the reasons that follow, Plaintiffs' experts' attempt to establish general causation through these observational studies must be rejected as unreliable.

A. Confounding by Indication Plausibly Explains Any Reported Association

Observational studies are not capable of establishing a valid statistical association between Lipitor and diabetes. "For small to moderate effect sizes," such as the purported effect of Lipitor on diabetes, "all observational analytic studies, no matter how well designed, conducted, analyzed, and interpreted, are hypothesis formulating."[10] This is so because "their inherent uncontrolled and uncontrollable confounding can be as big as the effect sizes" being explored, making it impossible to rule out confounding as a potential source of the association.[11] Before reversing course, Dr. Singh required a risk ratio of more than 1.5, "at least demonstrating

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[9] Navarese (2013) [972-48] at 1127.
[10] Hennekens & DeMets (2011) (Ex. 103) at 1134.
[11] *Id.*

a 50 percent increase in hazard," as a threshold for considering a "more likely causal" association in an observational study. Singh Tr. [972-3] at 349:1-350:20; Singh Rpt. [972-6] at 34.

[redacted] *see* Elasy Supp. Rpt. (Ex. 99) at 4. It arises because the individuals who are prescribed a drug are inherently different from those who are not and because the factors associated with the prescription of the medication are also associated with the outcome of interest. Hennekens Supp. Rpt. (Ex. 98) at 13. For "all observational studies of small to moderate effects involving pharmacologic therapies, confounding by indication always represents a plausible alternative explanation for any observed finding." *Id.*; *see* Elasy Supp. Rpt. at 9. Other courts have recognized the problem of confounding by indication in observational studies of pharmaceutical therapies. *Zoloft*, 2015 WL 7776911, at *14; *Zoloft*, 26 F. Supp. 3d at 465.

In studies of statins and diabetes, "confounding by indication arises because the prescribing physician is more likely to prescribe a statin for those patients at higher risk of developing diabetes …, because these are the same patients who are at highest risks" for the cardiovascular events that are "the chief indication, or reason, for which the statin is prescribed." Hennekens Supp. Rpt. (Ex. 98) at 4; [redacted]. There is substantial overlap in the risk factors for diabetes and cardiovascular disease, including age, BMI, physical inactivity, hypertension, high LDL cholesterol, low HDL cholesterol, and high triglycerides. Hennekens Supp. Rpt. at 4; [redacted] Because the indications for statins and the risk factors for diabetes are similar, "[n]o matter how low the p value or how narrow the confidence intervals, as well as even after adjustment for all the correlates of prescribing habits, it is not possible to exclude residual confounding by indication as a plausible alternative explanation for any observed findings." Hennekens Supp. Rpt. at 4; [redacted]. "Thus, any reported increase in the risk of diabetes is not necessarily due to the drug, but rather to the risk factors of the patient, which, in

turn, increase the likelihood of being prescribed the drug and then observing a statistically significant increase in diabetes among those prescribed the statin." Hennekens Supp. Rpt. at 4. Indeed, observational studies "should be expected to show an increased risk of diabetes in those prescribed statins." *Id.* at 5. "If this did not occur, then one would conclude that prescribing physicians are not giving the drug to those who need it the most." *Id.*

Though Dr. Singh omits entirely from both of his reports any reference to "confounding by indication,"[redacted].[12] [redacted] So, too, due to their many inherent limitations, inferences from all observational studies "should be interpreted with caution." Singh Supp. Rpt. (Ex. 92) at 29; [redacted]

Plaintiffs' other experts make similarly fatal concessions on the inherent limitations of observational studies. For instance, Dr. Gale, from whom Plaintiffs have not solicited a supplemental report, agrees that observational studies are "notoriously easy to criticize," Gale Tr. [972-1] at 223:5-16, are hypothesis-generating only, and "don't address the question of causation." *Id.* at 219:4-221:1. Dr. Roberts, who previously opined that observational studies present better data than clinical trials, Roberts Tr. [972-9] at 110:17-111:2, 176:11-18, admits that her 2012 book states that "[o]bservational studies may tell us about association but they cannot prove causation." Roberts, *The Truth About Statins* (2012) (Ex. 102) at 106; Roberts Supp. Tr. (Ex. 97) at 490:5-24. Even Dr. Quon, [redacted]

[12] Kwok et al., *Statins and associated risk of pneumonia: a systematic review and meta-analysis of observational studies*, 68 Eur. J. of Clin. Pharm. 747, 753 (2015) (Ex. 105); Chelladurai et al., *Venous thromboembolism prophylaxis in patients with traumatic brain injury: a systematic review*, 2 F1000 Res. 132, at 11 (2013) (Ex. 106); Singh & Loke, *Drug safety assessment in clinical trials: methodological challenges and opportunities*, 13 Trials 138, at 3-4 (2012) (Ex. 107).

[redacted] admits that "observational studies are among the weakest type of evidence" and, rather than proving causation, they "form[] the basis for developing a hypothesis." Quon Tr. [972-2] at 296:16-297:2.

In sum, confounding by indication exists in all observational studies of the hypothesized association between Lipitor and newly diagnosed diabetes and is about as big as the effect sizes being explored. All such studies, no matter how large, well designed, conducted and analyzed, "should be considered, at best, hypothesis formulating and, at worst, misleading, due principally to uncontrolled and uncontrollable confounding by indication." Hennekens Supp. Rpt. (Ex. 98) at 4, 13, 19, 24. Further examination of the many limitations of the observational studies on which Plaintiffs' experts rely makes this even more apparent.

B. Plaintiffs' Experts' Observational Studies Cannot Reliably Show Causation

Plaintiffs' experts proffer several observational studies that they submit furnish reliable evidence of general causation at doses less than 80 mg.[13] These studies are Cederberg, Chen, Culver, and Carter, as well as others cited only by Dr. Roberts. Of these observational studies, only Cederberg reports any, albeit limited, dosage-specific data on newly diagnosed diabetes in Lipitor users compared to non-users of statins. Moreover, Dr. Singh candidly admits that [redacted]

[13] Though Dr. Singh repeatedly denies that any observational studies "report on the risk of diabetes with [Lipitor] 10 mg," Singh Supp. Rpt. (Ex. 92) at 4, 28, 29, Cederberg and Izzo (which Plaintiffs' experts ignore) find no statistically significant association with diabetes at that dose. Izzo et al., *Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk*, 11 Nutr. Metab. Cardiovasc. Dis. 1101 (2013) (Ex. 108). Dr. Singh admits that [redacted]

[redacted] The studies Plaintiffs' experts cite are inherently and fatally marred by confounding by indication, as well as by many other flaws. They cannot reliably show a valid statisistical association.

1. Cederberg

The Cederberg observational study[14] reports a statistically significant 1.37 relative risk for a combined 20 mg and 40 mg Lipitor group, but no significant risk for 10 mg. Cederberg "shows just how different statin users are from non-users in terms of underlying features of pre-diabetes or insulin resistance, and why observational studies of [Lipitor] and diabetes remain highly confounded and therefore unreliable." Waikar Supp. Rpt. (Ex. 100) at 6. For many reasons – including lack of generalizability, confounding by indication, failure to adjust, and low relative risk – Cederberg cannot reliably show a valid statistical association, let alone causation.

Lack of Generalizability: As a study in Finnish men, the Cederberg authors caution that "the applicability of these results to women or to other ethnic groups remains unknown,"[15] [redacted] Further, the study lacks internal validity. 37% of the subjects in the cohort were lost to follow-up, such that "observation bias is a plausible alternative explanation for any observed findings." Hennekens Supp. Rpt. (Ex. 98) at 19; [redacted] Moreover, only 55% of subjects "had fasting blood sugar analyses performed during follow-up," which "is even lower than the overall follow-up rate." Hennekens Supp. Rpt. at 20. Thus, "an opposite result could easily have been detected among the subjects lost to follow-up, leading to completely null results." *Id.* [redacted][16] Moreover, while only Cederberg purports to evaluate 20-40 mg, it is unknown how many subjects were prescribed (a) 20 mg or (b) 40 mg of Lipitor. Only their sum

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[14] Cederberg et al., *Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort*, 58 Diabetologia 1109 (2015) [1159-1] at 8.

[15] Cederberg (2015) [1159-1] at 8.

[16] *Id.* at 5.

is provided. Nor are any data reported for the subjects who were prescribed 80 mg of Lipitor.

Confounding by Indication: Confounding by indication in a particular problem in Cederberg because it is a study in subjects with components of the metabolic syndrome (the Metabolic Syndrome in Men (METSIM) cohort),[17] which carries an increased risk for diabetes. [redacted]; Waikar Supp. Rpt. (Ex. 100) at 12-14. This limitation has been recognized in a recent peer-reviewed, published paper, which explains that Cederberg "could be subject to substantial confounding by indication," given that "statin recipients clearly already differed substantially from non-recipients in characteristics at baseline, before the onset of diabetes."[18] The problem of confounding by indication is particularly acute for those subjects on Lipitor because Lipitor in general, and higher doses in particular, are preferentially prescribed for patients at highest risk of developing diabetes. Hennekens Supp. Rpt. (Ex. 98) at 5, 20; [redacted]

Failure to Adjust: While Cederberg purported to adjust for certain confounding factors, it did not and could not adjust for them all. [redacted] "[I]t is peculiar that data on hypertension would not be available in a study that focused on metabolic syndrome," Elasy Supp. Rpt. (Ex. 99) at 8, since hypertension is a component of metabolic syndrome and, thus, highly likely to be both present and measurable in the study population at baseline. *Id.*

Moreover, Cederberg's method of adjustment was unconventional and unreliable. Rather than evaluating each individual factor separately and then building a model to control all the variables simultaneously, Cederberg presented 14 different models, each separately adjusting for different factors. Hennekens Supp. Rpt. (Ex. 98) at 21-22; *see* Roberts Supp. Tr. (Ex. 97) at 511:12-19. For example, Cederberg reported its adjusted relative risk for the combined 20 and

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[17] *Id.* at 1.

[18] Livingstone et al., *Effect of atorvastatin on glycaemia progression in patients with diabetes: an analysis from the Collaborative Atorvastatin in Diabetes Trial (CARDS)*, 59 Diabetologia 299, 300, 305 (2015) (Ex. 109).

40 mg doses based only on model 2.[19] Model 2 did not adjust for confounders such as baseline blood glucose level, weight gain, and triglycerides, [redacted] Waikar Supp. Rpt. (Ex. 100) at 17, some of the most significant risk factors for diabetes. Defs. Br. [972] at 12-14. [redacted] Cederberg presents consistently biased overestimates of any association between statins and diabetes that are most plausibly due to confounding by indication. Hennekens Supp. Rpt. at 22; Elasy Supp. Rpt. (Ex. 99) at 9.

Limited Dose Information: Cederberg did not find a statistically significant association at 10 mg.[20] [redacted], that is methodologically unsound, Hennekens Supp. Rpt. (Ex. 98) at 35, and courts have rejected, as unreliable, attempts to extrapolate a causal inference from non-significant "trends." *Zoloft*, 26 F. Supp. 3d at 461-62.

Further, while Cederberg reported a statistically significant association by combining the 20 and 40 mg doses, and is the single study that assesses 20-40 mg, the data are not separated between the two doses.[21] [redacted], or whether there was a dose-response between those two doses. Roberts Supp. Tr. (Ex. 97) at 515:7-15. Nor can any dose-response inference be drawn from the handful of 80 mg patients in the study, for whom no findings were reported. Hennekens Supp. Rpt. (Ex. 98) at 21.

Low Relative Risk: Even if Cederberg's reported 1.37 association for the combined 20 mg and 40 mg doses were valid (and it is not), it does not meet Dr. Singh's threshold of greater than 1.5 for an observed association that "is considered more likely causal." Singh Rpt. [972-6]

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[19] Cederberg (2015) [1159-1] at 3.
[20] *See id.*
[21] Cederberg (2015) [1159-1] at 3.

at 34. Dr. Singh adopted that threshold in his original report because it was said to be used by "statisticians who work with [him] and lots of other people." Singh Tr. [972-3] at 349:1-350:20. Now confronted with associations of less than 1.5, he claims that [redacted] To the contrary, the Court should find that, under the standard adopted by Dr. Singh before the instant inquiry into dose, the association reported by Cederberg cannot reliably show causation. [redacted]

2. Chen

Plaintiffs' experts also cite the Chen observational study, which reported a statistically significant association between statins and new diabetes diagnoses.[22] Chen was a case-control study conducted in an insurance claims database for a unique, non-generalizable Asian population. Singh Rpt. [972-6] at 20, 45. That Chen was conducted in an insurance database limits the reliability of its findings since "case-control or cohort study data collected for administrative purposes, no matter how large in sample size, should be considered hypothesis formulating."[23] [redacted] *see* Elasy Supp. Rpt. (Ex. 99) at 6. Chen also poses a problem of fit. Though

[22] Chen et al., *Differential Impact of Statin on New-Onset Diabetes in Different Age Groups: A Population-Based Case-Control Study in Women from an Asian Country*, PLoS ONE, Aug. 2013 [1159-21] at 5. Dr. Quon does not cite Chen, which reported a higher risk for pravastatin (which Dr. Quon believes reduces the risk of diabetes) than for Lipitor.

[23] Hennekens & DeMets (2011) (Ex. 103) at 1134.

Dr. Roberts mistakenly identified Chen as reporting a relative risk specific to the 10 mg dose, Roberts Supp. Tr. (Ex. 97) at 439:7-12, Chen reports no dose-specific results for Lipitor, making it incapable of satisfying the Plaintiffs' burden under CMO 49. [redacted] Elasy Supp. Rpt. at 4. [redacted]

Despite Dr. Singh's misgivings, he and Dr. Roberts try to extrapolate a dose-specific relative risk from Chen's findings on cumulative dose. Singh Supp. Rpt. (Ex. 92) at 8; Roberts Supp. Rpt. (Ex. 94) at 6. Yet the cumulative dose findings "were only significant for … the highest dose-duration category," giving them no relevance to lower doses. Singh Supp. Rpt. (Ex. 92) at 8. Chen also failed to adjust for many confounders, including ethnicity, impaired fasting glucose, impaired glucose tolerance, family history, physical inactivity, BMI, metabolic syndrome, smoking, and diet. Singh Tr. [972-3] at 246:10-251:2. [redacted] "Further, the failure to control confounding by body weight" – one of the greatest risk factors for diabetes – "renders any analysis of diabetes to be uninterpretable." Hennekens Supp. Rpt. (Ex. 98) at 24. Chen also illogically purports to adjust for "diabetes" when analyzing the risk of diabetes. Roberts Supp. Tr. (Ex. 97) at 539:7-17; Elasy Supp. Rpt. (Ex. 99) at 6. If there is any doubt as to the unreliability of its findings, Chen reported a similar, if not larger, significant association between aspirin and diabetes than for Lipitor. Roberts Supp. Tr. at 533:13-22; Elasy Supp. Rpt. at 6.

3. Culver

Plaintiffs concede that the Culver[24] observational sub-study from the Women's Health Initiative "did not have access to dose information and thus the paper does not provide direct evidence that Lipitor causes diabetes at lower doses." [1159] at 8. [redacted]

[24] Culver et al., *Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative*, 172 Arch Intern Med 144 (2012) [1159-16]. Like Chen, Dr. Quon did not cite Culver.

[redacted] *see* Hennekens Supp. Rpt. (Ex. 98) at 18-19. Dr. Singh acknowledged that Culver must be interpreted cautiously because it did not adjust for many critical confounders, including hypertension, metabolic syndrome, impaired fasting glucose, and impaired glucose tolerance. Singh Tr. [972-3] at 208:11-17, 232:2-7. When the available data were adjusted for baseline fasting glucose in a sensitivity analysis, statins were "not significantly related" to diabetes (HR 1.06; 95% CI 0.61-1.86).[25] Culver cannot show a true association.

4. Carter

The design of the Carter[26] study – a cohort analysis of a claims database for prescription drugs dispensed to individuals over 65 – presents two substantial limitations. First, because Carter, like Chen, was conducted in an insurance claims database, its results are, at most, only hypothesis generating. Hennekens Supp. Rpt. (Ex. 98) at 23. Second, because all individuals in the claims database received medications, Carter compared the risk of diabetes from various statins to another statin (pravastatin), not to a placebo group. As a result, Carter cannot reliably show any risk of new diabetes diagnoses attributable to Lipitor. *Id.*

Further, Carter is unreliable. The study's findings that the relative risks for each statin were directly proportional to the statin's potency is most plausibly explained by confounding by indication. That is, "confounding by indication has resulted in the patients at highest risk of diabetes being prescribed the most efficacious statins, Lipitor and Crestor, those at intermediate risk being prescribed Zocor, and the lowest risk prescribed Lescol or Mevacor." Hennekens Supp. Rpt. (Ex. 98) at 23; [redacted]. The risk of such confounding is especially acute. Carter failed to adjust for weight, ethnicity, family history, baseline elevated blood glucose, physical activity, triglyceride concentrations, and blood lipids. Singh Tr. at 258:25-262:1. As with Chen, Carter failed to adjust for body weight and, thus,

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[25] *Id.* at 147. Only 3,706 out of 153,840 study participants had data available for baseline fasting glucose. *Id.*

[26] Carter et al., *Risk of incident diabetes among patients treated with statins: population based study*, BMJ, May 2013 [1159-15] at 1.

suffers from a major limitation. Singh Rpt. [972-6] at 46; Hennekens Supp. Rpt. at 23.

5. Mansi and Macedo

Finally, Dr. Roberts relies on two other observational studies – Mansi[27] and Macedo[28] – that she says show that Lipitor causes diabetes across the dosage range. Neither can do so. In fact, neither even reports a finding specific to any dose of Lipitor.

Even if Dr. Roberts's reliance on Mansi was not precluded because it was not cited in her prior report or in Plaintiffs' briefing in response to the Court's September 25, 2015 Order [1271], it cannot meet Plaintiffs' burden since Mansi does not report findings specific to any statin, much less specific to any dose. Roberts Supp. Tr. (Ex. 97) at 440:11-14; Elasy Supp. Rpt. (Ex. 99) at 10.[29] Moreover, Mansi suffers from many of the same problems as the other studies. Only 19% of the study subjects took Lipitor. Mansi's data were drawn from a claims database, limiting its use to hypothesis generation. It also failed to measure or adjust for many diabetes risk factors such as BMI, weight gain, ethnicity, family history, activity levels, diet, HbA1c, impaired fasting glucose, impaired glucose tolerance, triglycerides, and metabolic syndrome. Roberts Supp. Tr. at 549:7-551:14; Elasy Supp. Rpt. at 12; Hennekens Supp. Rpt. (Ex. 98) at 40.

Macedo reports no data specific to Lipitor, let alone any specific dose. Macedo did not adjust for many risk factors such as weight or obesity, baseline glucose, HDL, triglycerides, metabolic syndrome, or hypertension. Roberts Supp. Tr. (Ex. 97) at 573:7-574:11. Further, the authors admonish that their "findings should be interpreted with caution as observational studies are subject to residual ***confounding by indication*** and other biases that cannot be ruled out."[30]

In sum, the observational studies cited by Plaintiffs' experts confirm the uncontrollable problems of confounding by indication inherent in such data. The small effect size reported in these studies precludes their use to establish a valid statistical association and, thus, negates their

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[27] Mansi et al., *Statins and New-Onset Diabetes Mellitus and Diabetic Complications: A Retrospective Cohort Study of US Healthy Adults*, 30 J. Gen. Intern. Med. 1599 (2015) (Ex. 110).

[28] Macedo et al., *Statins and the risk of type 2 diabetes mellitus: Cohort study using the UK Clinical Practice Research Datalink*, 14 Cardiovasc. Disord. 85 (2014) (Ex. 111).

[29] *See* Mansi (2015) (Ex. 110).

[30] Macedo (2014) (Ex. 111) at 10 (emphasis added).

ability to show causation under the Hill factors.[31] Not only does the limited dosage-specific observational data fail to meet Dr. Singh's threshold of greater than 1.5, but it also pales in comparison to well-established diabetes risk factors, such as obesity, which carries a relative risk of more than 20. Hennekens Supp. Rpt. (Ex. 98) at 26.[32] Plaintiffs' experts' causation opinions based on these studies are unreliable.

III. GLUCOSE CHANGE DATA CANNOT RELIABLY SHOW GENERAL CAUSATION

A. Glucose Studies Cannot Reliably Show Causation of Diabetes

In an attempt to overcome the absence of reliable evidence of causation from randomized clinical trials and observational studies, Dr. Quon claims that studies of glucose levels show that Lipitor causes diabetes at all doses. *See* Quon Supp. Rpt. (Ex. 93) at 5-8. As this Court previously observed, "whether a single elevated glucose measurement can be used as a proxy for new-onset diabetes (Plaintiffs' alleged injury in this lawsuit) is suspect." CMO 54 [1258] at 7. There is a similar "analytical gap" in Dr. Quon's opinion, [redacted] *Joiner*, 522 U.S. at 146.[33]

The studies that Dr. Quon relies on are not suited to showing causation. They have many of the same methodological limitations that make the NDA glucose data unreliable to show causation of diabetes. They are studies of short duration, in small populations, with baseline glucose abnormalities, evaluating glucose changes, not diabetes. For instance, Dr. Quon relies heavily on Koh (2010), which he co-authored. Koh was a two-month trial in five groups of 44 patients with average glucose in the prediabetic range comparing glucose changes from various

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[31] Hill, *The Environment and Disease: Association or Causation*, 58 Proc. Royal Soc'y Med. 295, 295 (1965) [972-32].

[32] Colditz et al., *Weight as a risk factor for clinical diabetes in women*, 132 Am. J. Epidemiol. 501, 483 (1990) [1004-46].

[33] In addition to the absence of a valid association, this evidence cannot satisfy the analysis required by the Hill factors. For example, the short timeframe of these studies precludes their use to prove causation of a progressive disease that takes at least a decade to develop, the small increases in glucose they report do not show a strong association, and the body of mechanistic evidence is inconsistent both internally and with other evidence. *Cf.* Hill (1965) [972-32] at 295-98; Hennekens Supp. Rpt. (Ex. 98) at 26.

doses of Lipitor to placebo.[34] [redacted] "Small randomized controlled studies like the Koh study are susceptible to biased findings due to chance imbalances across study groups." Waikar Supp. Rpt. (Ex. 100) at 30. Koh's results were also internally inconsistent, indicating a questionable association. The increases in HbA1c in the Lipitor groups compared to placebo were statistically significant only at certain doses (not 10 mg), and "a significant portion of these patients in all groups either had diabetes or metabolic syndrome at baseline making a comparison of HbA1c changes difficult." Elasy Supp. Rpt. (Ex. 99) at 23. Moreover, none of the increases in glucose compared to placebo were significant.[35] Thus, "there is absolutely no effect on reported fasting glucose values. Zero." *Id.* at 13; [redacted]

Further, Dr. Quon does not simply rely on these glucose studies in an attempt to show causation for doses less than 80 mg, he relies on them without explaining how they can be reconciled with the contrary findings in the clinical trial data outlined above. Where epidemiological data, such those from randomized clinical trials, "does not support the conclusions drawn by the experts, the experts must endeavor to reconcile the inconsistent epidemiological data with their opinions." *In re Zoloft (Sertraline Hydrocloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 476 (E.D. Pa. 2014). Dr. Quon's opinion, in contrast, is based on the fallacious inference that positive findings in glucose change data may undermine and replace negative and null findings in the clinical trial data. Dr. Singh admits that these types of studies "should be interpreted with caution" in the absence of supporting data from clinical trials, Singh Supp. Rpt. (Ex. 92) at 29, [redacted]. Dr. Quon's attempt to use physiological studies for more than that limited purpose is unreliable.

Though it is not apparent from Dr. Quon's supplemental report, the totality of the data on

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[34] Koh et al., *Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients*, 55 J. Am. Coll. Cardiol. 1209, 1210 (2010) (Ex. 112).

[35] *Id.* at 1212, 1213, 1215, fig. 2.

which he relies is conflicted and inconsistent. Dr. Quon finds support for his opinions in this literature only by analyzing it with a results-oriented methodology that disregards his statements in peer-reviewed papers. For instance, Dr. Quon co-authored Koh (2011),[36] a paper that reviewed the extant literature on Lipitor's effect on insulin sensitivity. 8 of 9 cited studies did not report any adverse metabolic effect of Lipitor.[37] Dr. Quon and his co-authors stated "[i]t is not clear why [Lipitor] has beneficial metabolic actions in some studies but not in others."[38]

Unlike Koh (2011), [redacted]

Dr. Quon misapprehends his role as an expert witness. "Scientists are expected to address and reconcile data that does not support their opinions, and not simply rely upon data which does." *Zoloft*, 2015 WL 7776911, at *7; *see Bextra & Celebrex*, 524 F. Supp. 2d at 1177; *Rezulin*, 309 F. Supp. 2d at 563. Where the body of scientific evidence is inconsistent, an expert "must thoroughly analyze the strengths and weaknesses" of that evidence and explain why contrary studies do "not contradict or undermine their opinion." *Zoloft*, 26 F. Supp. 3d at 475.

[redacted]

[36] Koh (2011) (Ex. 101).
[37] *Id.* at 3-4, tbl. 2.
[38] *Id.* at 4.

[redacted] That his opinions "are drawn from trends [he] observed in a self-selected subset of supportive studies, not the totality of the epidemiological evidence, further underscores [his] problematic methodology." *Zoloft*, 26 F. Supp. 3d at 461-62.[39]

[redacted]

[39] Like Dr. Quon, Dr. Singh cites only the physiologic studies that (he says) support his opinion. Singh Supp. Rpt. (Ex. 92) at 10.

[redacted] was, in fact, what he stated directly in his published Koh (2011) paper – that Lipitor "has beneficial metabolic actions in some studies but not in others," and it is unclear why.[40] At his deposition, [redacted]

[redacted]

Dr. Quon does not follow the same scientific principles in the courtroom that he does in his professional work. In his published articles, he purports to consider the totality of evidence, but in litigation, he discusses only the studies that (he says) support his opinion. He rationalizes his decision to ignore contrary studies by calling them "flawed," but fails to identify any flaw in any study. He argues that to [redacted] He rejects his published work by invoking an unpublished and inscrutable "deep" knowledge of the real truth that aligns with the position of the party that retained him. He violates the principle that an expert must "employ[] in the courtroom the same level of intellectual rigor that characterizes the

[40] Koh (2011) (Ex. 101) at 4.

practice of an expert in the relevant field," *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999), and engages in "situational science" that is antithetical to *Daubert*'s standards for reliability. *Zoloft*, 2015 WL 7776911, at *10-11. His testimony should be excluded.

B. NDA and Safety Update Data Cannot Reliably Show Causation

[redacted] Though they fastidiously avoid referencing Dr. Jewell, they commit the same methodological errors identified by this Court in its order excluding his analysis of the NDA data. These opinions should be barred.

1. Glucose Data Cannot Be Extrapolated to Diabetes

Plaintiffs' continued reliance on the 1996 NDA and the 1999 and 2001 Safety Updates remains a non-starter. [redacted] as this Court held with regard to the NDA data, they cannot provide a reliable basis on which to opine that Lipitor causes new-onset diabetes.

> [W]hether a single elevated glucose measurement can be used as a proxy for new-onset diabetes (Plaintiffs' alleged injury in this lawsuit) is suspect.
> …
> Plaintiffs state a single elevated glucose measurement is insufficient to infer diabetes. (Dkt. No. 1159 at 12). Therefore, even if the methodological flaws discussed below were not present, the Court would exclude Dr. Jewell's opinion that this data 'should have alerted Parke-Davis and Defendant to the possibility of increased risk of new-onset diabetes associated with atorvastatin treatment." (Dkt. No. 1247-9 at ¶ 6).

CMO 54 [1258] at 7, 8-9.

Plaintiffs' supplemental expert reports provide no basis to relitigate this issue. [redacted]

[redacted] But Dr. Roberts – who is "not an expert in diabetes," *id.* at 376:3-5 – could provide no basis for these *ipse dixit* statements and ultimately conceded that more than one such measurement is required for a diabetes diagnosis. *Id.* at 578:14-17. [redacted]

Dr. Singh condeded the point outright. [redacted] Dr. Singh characterizes these documents as "indirect evidence [that] will be down weighted." *Id.* at 2. Dr. Singh further emphasizes that any "hypothesis" based on these data "needs to be interpreted with caution." *Id.* at 11. Dr. Singh's "hypothesis" is that if a valid association with new-onset diabetes were otherwise established at each Lipitor dose, [redacted]

2. Failure to Analyze Underlying Data or Account for Confounding

[redacted] Mr. Goldman is a litigation consultant retained by Plaintiffs' counsel who also assisted Drs. Jewell and Abramson in preparing their reports. Jewell Tr. [972-7] 390:2-391:13, 393:12-394:2, 396:17-21; Abramson

Tr. [972-4] [972-8] at 258:25-265:12, 329:21-330:8. Given that Mr. Goldman fact-checked Dr. Jewell's statistical analyses of the NDA, Jewell Tr. at 390:19-391:13, he presumably had access to patient-level data. [redacted]

Because they chose not to review patient-level data, Plaintiffs' experts failed to discern or address that the vast majority of 10 mg patients reported as having glucose elevations were already diabetic at baseline. [redacted]

[redacted] Roberts Supp. Tr. (Ex. 97) at 431:2-8. Yet the patient-level data from the NDA studies "prove[] this assumption false." CMO 54 [1258] at 12. [redacted]

Dr. Quon offers another rationale. He opines that "[i]t is important not to exclude from analysis patients who already have diabetes before Lipitor treatment because Lipitor causes insulin resistance and hyperglycemia in a certain fraction of patients regardless of whether they have diabetes or not." Quon Supp. Rpt. (Ex. 93) at 36. [redacted] "This is important because glucose levels are not only higher in patients with diabetes, these patients have fluctuations in glucose levels that are more extreme than patients without diabetes." Elasy Supp. Rpt. (Ex. 99) at 17. Dr. Quon's circular reasoning cannot negate the "potential for confounding" previously recognized by this Court. CMO 54 [1258] at 10-11.

3. Dr. Quon's "Baseline Comparison" Methodology Is Unreliable

In analyzing the NDA and Safety Updates, Dr. Quon opines that the cause of Lipitor patients' glucose elevations can be determined in two different ways: (a) comparing the incidence of glucose elevations among Lipitor and placebo patients, and (b) comparing Lipitor patients' glucose levels during the trials with their own baseline glucose values. *See* Quon Supp. Rpt. (Ex. 93) at 36-37. Of these, Dr. Quon opines that "the most relevant comparison is to the patients' own baseline where they ***serve as their own control*** and minimize other external

variables." *Id.* at 36 (emphasis added). [redacted]

Dr. Quon's opinion is inadmissible. [redacted] The evidence belies any such assumption. "There are two circumstances in which patients act as their own control: crossover designs and pre-test/post-test designs."[41] None of the relevant Lipitor clinical trials used these designs. Moreover, these designs are inappropriate for patients with progressive diseases. *See TPM* at 209-10. Where, as here, patients entered the studies with progressive glucose disorders and/or diabetes, "we need concurrent randomised controls" to "disentangle the treatment effect" from the natural progression of that baseline condition. *Id.* at 210. [redacted]

Nor did Dr. Quon follow his "baseline comparision" methodology. Doing so would require comparing patients' baseline and treatment values. For example, "[i]n a pre-test/post-test design, each individual subject is measured on two occasions separated by the same treatment and the difference between the two measurements, appropriately averaged across subjects, is an estimate of the effect of treatment." *TPM* at 210. [redacted]

[41] Griffin, *The Textbook of Pharmaceutical Medicine*, at 209 (7th ed. 2013) ("*TPM*"). "Pre-test/post-test" refers to a single-group design, *i.e.*, one with no "concurrent randomised controls." *Id.* at 210.

[redacted]

Dr. Quon also applied his "baseline comparison" methodology in a selective, results-driven manner that is "unacceptable under *Daubert* and Rule 702." CMO 54 [1258] at 22. [redacted] In sum, Dr. Quon proffers an unreliable "baseline comparison" methodology that he applies selectively and at his whim to bolster his methodologically flawed analysis of the "placebo comparison" data. His testimony should be excluded.

IV. THE FDA LABEL CHANGE IS NOT RELIABLE EVIDENCE OF CAUSATION

Some of Plaintiffs' experts claim that the absence of any dose parameters in the FDA's warning regarding reports of increased glucose with Lipitor "is proof that close examination of the data by regulators did not consider any such differences in doses to be meaningful." Singh Supp. Rpt. (Ex. 92) at 24; *accord* Roberts Supp. Rpt. (Ex. 94) at 1. This contention is flawed.

Arguing that differences in dose are not meaningful is contrary to Plaintiffs' prior position, where they "argue[d] emphatically that their 'experts *did* find a dose-response relationship.'" CMO 49 [1197] at 3-4. Further, Plaintiffs' experts cite nothing in support of their belief that the absence of a dose restriction in the FDA's warning indicates its determination there was no difference as to dose. In any event, it is unreliable to draw any scientific inferences about causation from the FDA's regulatory decisions. Dr. Roberts was notably unaware of what standard the FDA applies to such decisions. Roberts Supp. Tr. (Ex. 97) at

619:3-6. But it is well settled that "[t]he FDA evaluates pharmaceutical drugs using a different standard than the causation standard" for a tort claim and will act "upon a lesser showing of harm to the public than the preponderance-of-the-evidence or more-likely-than-not standards used to assess tort liability." *Glastetter*, 252 F.3d at 991. The FDA's balancing of risk and benefit in a warning for a prescription medication "is irrelevant in determining the threshold question" of general causation. *Id.; see McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1249-50 (11th Cir. 2005); *Meade v. Parsley*, 2010 WL 4909435, at *8 (S.D. W. Va. 2010). The FDA label change cannot satisfy Plaintiffs' burden to prove general causation on a dose-by-dose basis.

CONCLUSION

No randomized clinical trial, observational study, or otherwise reports a statistically significant association between 10 mg and diabetes. Physiological studies and glucose data are not reliable evidence of causation for the reasons set forth above and by the Court in CMO 54. There is no reliable evidence for general causation at 10 mg.

There is no randomized clinical trial data from large-scale studies at 20 mg or 40 mg. Dr. Singh admits that if he cannot establish causation at 10 mg, then he cannot establish causation at 20 mg or 40 mg. The observational studies at issue cannot establish a valid association, or causation, due to confounding by indication and many other limitations. Nor can the physiological studies, NDA, or Safety Updates, reliably show causation at 20 or 40 mg.

Plaintiffs' experts cannot reliably show general causation at 80 mg by relying on *post hoc* analyses of clinical trial data that ignores the totality of clinical trial data, which is inconsistent, as well as published meta-analysis reporting no significant risk at any dose. The other sources of data cannot reliably establish general causation for the reasons set forth above. Thus, there is no reliable evidence for general causation at 80 mg.

For the foregoing reasons and those set forth in Pfizer's prior briefing and at the hearing, Pfizer's motion to exclude Plaintiffs' general causation evidence should be granted.

Dated: February 12, 2016

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that, this 12th day of February, 2016, I have electronically filed a copy of the above and foregoing with Clerk of the Court using the ECF system, which sent notification of such filing to counsel of record.

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